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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,317	03/09/2001	Ruoying Tan	6514-090US1	7596

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EXAMINER
BYRD, DEVON R

ART UNIT	PAPER NUMBER
1639	10

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/803,317	TAN ET AL.	
	Examiner	Art Unit	
	Devon R Byrd	1639	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 and 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

Claims 1-26 are pending in this application and subject to restriction/election of species. Of the above claims, 18-26 are withdrawn from consideration as they are directed to non-elected Groups.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-17, drawn to a method of identifying a nucleic acid encoding a signal sequence, classified in class 435, subclass 91.41.

II. Claims 18-20, drawn to a high throughput method of identifying a cDNA which encodes a secreted protein, classified in class 435, subclass DIG 17.

III. Claims 21 and 22, drawn to a method for detecting a protein comprising a signal sequence, classified in class 435, subclass 4.

IV. Claims 23-26, drawn to a vector for identifying a cDNA insert encoding a protein comprising a signal sequence, classified in class 435, subclass 320.1.

The inventions are distinct, each from the other because of the following reasons:

Groups IV and Groups I-III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the vector of Group IV can be used in either of the methods of

Groups I, II, or III. The methods of Groups I-III can be practiced using a vector different from that of Group IV, such as a vector lacking a eukaryotic promoter element.

Groups I and II are different and patentably distinct methods because they involve different method steps, require different reactions and/or conditions, and/or produce different results. For example, the method of Group I requires a single cDNA, whereas the method of Group II requires a plurality of cDNAs. The method of Group II requires that the introduction of a cDNA into a vector produces a cDNA-β-lactamase fusion, not required in the method of Group I.

Groups I and III are different and patentably distinct methods because they involve different method steps, require different reactions and/or conditions, and/or produce different results. For example, the method of Group I does not requires the detection of a protein as claimed in Group III, merely the persistence of bacterial cells in a selective growth medium.

Groups II and III are different and patentably distinct methods because they involve different method steps, require different reactions and/or conditions, and/or produce different results. For example, the method of Group III requires a single cDNA, whereas the method of Group II requires a plurality of cDNAs. The method of Group II requires that the introduction of a cDNA into a vector produces a cDNA-β-lactamase fusion, not required in the method of Group III.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Carol Francis on August 4, 2003 an election was made with traverse to prosecute the invention of Group I, claims 1-17. Further, applicant's election with traverse of the following species- pBK vector, a lac promoter and a CMV promoter, beta-lactamase- in Paper No. 7 is acknowledged. The traversal is on the ground(s) that applicant was required to elect a single promoter, when in certain embodiments, two promoters were claimed. The previous examiner's species election requirement reads as follows: '...applicant is required to elect an ultimate species of vector that identifies the **promoters** and leaderless...'. As applicant's response meets the conditions of the previous examiner's requirement, the election has been treated as an election without traverse.

The requirement is still deemed proper and is therefore made FINAL.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 18-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the limitation "*the cDNA-**selection protein** fusion*" in line 15. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-6, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Stahl and Christiansen, Gene 71: 147-156, 1988 (hereinafter referred to as Stahl).

Stahl teaches a method of identifying a nucleic acid encoding a signal sequence, said method comprising:

- Directionally introducing (Figs.1-3 and p 151, col. 1 section (a), 1st ¶) each of a plurality of cDNAs into a vector (p 150, col. 2, 1st ¶) comprising a nucleic acid encoding leaderless [and therefore non-] secretable selection protein (Fig. 2, pLaC13-31 and p 148, col. 2, section (f)) wherein said introducing results in the formation of a cDNA-β-lactamase fusion nucleic acid in each of a plurality of vector molecules (Figs.1-3 and p 151, col. 1 section (a), 1st ¶);
- Introducing the plurality of vectors into bacterial cells to create a bacterial cell library (p 152, col. 2, 2nd ¶);
- Selecting bacterial cells containing a cDNA encoding a signal sequence by growth in a selective medium (p 151, section (b), 1st ¶, lns 1-4; p 152, col.2, 1st ¶, lns 1-3 and 2nd ¶, lns 1-5; and p 153, col. 1, bridging ¶, lns 7 and 8).

- Wherein the growth of the bacterial cells in said medium indicates that the cDNA comprises a signal sequence [thus providing a bacterial population enriched for proteins comprising signal sequences] (p 153, Table I).

Therefore, as discussed above, all of the claimed limitations have been anticipated by Stahl.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stahl, Moore et al., Analytical Biochemistry 247: 203-209, 1997 (hereinafter referred to as Moore), and Tashiro et al., Science 261:600-603, 1993 (hereinafter referred to as Toshiro).

Claims 1-8 are drawn to a method of identifying a nucleic acid encoding a signal sequence wherein a recombinant vector is provided comprising a cDNA fused [translationally in frame] to a nucleic acid encoding a leaderless [and therefore non-] secretable selection protein, wherein said selection protein is β-lactamase, producing transformed bacteria comprising said recombinant vector, growing said bacteria in a selective medium such that elaboration of a particular phenotype (e.g., survival in the presence of inhibitory concentrations of a β-lactam

antibiotic, e.g., ampicillin) indicates that said [formerly non-] secretable selection protein is now being secreted by virtue of protein sequences encoded by said cDNA.

As previously cited, all of the above limitations are taught by Stahl. Stahl does not teach the limitations of a dual expression vector, wherein the vector comprises a mammalian and a bacterial promoter, nor does Stahl teach subsequent analysis of bacterial hits in a eukaryotic system.

Claims 9-15 and 17 recite essentially the same method steps as in claims 1-8, but include subsequent analysis in eukaryotic (e.g., mammalian) cells transfected with vectors correlating to the bacterial hits. Said analysis is accomplished via detecting secretion of the protein fusion product in the cell culture.

Moore teaches vectors for use in methods of using β-lactamase as a reporter in mammalian cells (p203-204, bridging sentence), including the use of fusion constructs (p203, col 2, lns 19-22), wherein nitrocefin hydrolysis assays are used to detect β-lactamase. One of said vectors (pCMV-dBL) comprises a leaderless [and therefore non-] secretable selection protein, wherein said selection protein is β-lactamase, wherein said vector is a dual expression vector, wherein said vector comprises a mammalian (CMV) promoter (p 204, col 1, lns 8-11) and a bacterial (T7) promoter (as evidenced by Invitrogen electronic catalog entry for pRc/CMV).

Neither Stahl nor Moore expressly teach a multiple cloning site.

One of the vectors taught by Moore, pCMV-dBL, comprises bacterial gene expression signals that are appropriately positioned to enable the expression of translational fusion proteins encoded by nucleic acid molecules that are fused in frame with the leaderless β-lactamase segment. The use of a multiple cloning site to aid in constructing recombinant DNA molecules is

well known in the art, as is a bacterial selectable marker such as β-lactamase. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the vector and methods of Moore with the method of Stahl. One would have been motivated to do so for the purpose of verifying mammalian functionality for a sequence of non-bacterial origin (e.g., a mammalian cDNA library), wherein said sequence was initially identified in bacteria.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stahl and Moore as applied to claims 1-15 above, and further in view of Tashiro et al., Science 261:600-603, 1993 (hereinafter referred to as Toshiro).

Stahl and Moore do not expressly teach the limitation of 5' biasing of cDNAs.

Toshiro teaches a cloning strategy for secreted proteins comprising a signal sequence trap wherein each of a population of 5' biased cDNAs is cloned so as to generate a subpopulation of in-frame translational fusions with a nucleic acid encoding a signal peptide leader-less IL-2 receptor. Elaboration of the fusion-receptor on the cell surface, and its subsequent detection is indicative of a cDNA segment encoding a secretion signal sequence (p 600, columns 2-3, bridging ¶). Toshiro further teaches that the specific amino-terminal signal sequences that most precursors for secreted factors...carry...are within 400 base pairs (bp) of the 5' termini of the mRNA (p 600, col 2, 1st ¶, last sentence), thus rationalizing their 5' biasing of the input cDNA population (p 600 and 601, bridging ¶). It would have been obvious to one of ordinary skill in the art at the time the invention was made to clone the 5' biased population of cDNAs into the vector of Moore and use said cloned population in the methods of Moore and Stahl. One would have been motivated to do so in order to enrich for cDNAs representing 5' proximal mRNA segments,

because said segments would be more likely to encode amino-terminal signal sequences. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to subject the bacterial cells to a second round of selection in a selection medium. One would have been motivated to do this in order to decrease the incidence of false positives in the assay output.

Therefore, as discussed above, the invention of the above claims is prima facie obvious over Stahl in view of Moore, and in further view of Toshiro absent evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Devon R Byrd whose telephone number is 703-305-0159. The examiner can normally be reached on Mon-Fri 8a-5p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 703-306-2317. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-2742 for regular communications and 703-308-2742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

DB
August 25, 2003

BENNETT CELSA
PRIMARY EXAMINER